

## Different lengths of treatment with co-trimoxazole for acute uncomplicated urinary tract infections in women

T A M Trienekens, E E Stobberingh, R A G Winkens, A W Houben

### Abstract

**Study objective**—To compare three days' and seven days' treatment with co-trimoxazole in women with acute dysuria, strangury, and urinary frequency or urgency.

**Design**—Randomised double blind placebo controlled trial.

**Setting**—General practices in the south east of The Netherlands.

**Patients**—327 Non-pregnant female patients aged 12 to 65.

**Intervention**—161 Women were allocated to three days' treatment (co-trimoxazole 960 mg twice a day), and 166 women were allocated to seven days' treatment (co-trimoxazole 960 mg twice a day).

**Main outcome measure**—Resolution of symptoms at one, two, and six weeks.

**Results**—The rates for resolution of symptoms were not significantly different between the two groups. Cumulative rates of recurrence after three days' and seven days' treatment were 31/139 (22%) and 23/151 (15%) respectively six weeks after entry ( $p=0.16$ ). Adverse effects occurred in a quarter of women given three days' treatment compared with a third of women receiving seven days' treatment ( $p=0.29$ ). In only two patients did adverse effects necessitate stopping treatment.

**Conclusions**—Three days of co-trimoxazole seems to be as effective as a seven days' course for treating acute urinary tract infection in non-pregnant women.

### Introduction

The prevalence of acute uncomplicated urinary tract infection in women is fairly high at about 50/1000/year.<sup>1,2</sup> The optimal duration of antibiotic treatment, however, remains a point of discussion. Single dose treatment offers several advantages over the conventional duration, including improved compliance, reduced adverse effects, decreased risk of disturbing bacterial flora and selecting resistant micro-organisms, and lower costs.<sup>3,4</sup> In the past 20 years several studies have suggested that single dose treatment is as effective as the conventional regimens of 10 or 14 days.<sup>5,8</sup> No study, however, has included enough patients to prevent the type II error.<sup>9</sup> Freiman *et al*<sup>10</sup> and Fihn and Stamm,<sup>11</sup> reviewing 71 and 62 clinical studies respectively, concluded that most trials studied too few patients to detect a meaningful difference between the therapeutic regimens. In a recent study with adequate statistical power no symptomatic difference was observed between a single dose and 10 days of co-trimoxazole at three and 13 days and six weeks after the start of treatment.<sup>12</sup> Adverse effects, however, were twice as common in the group allocated to 10 days of treatment compared with the patients receiving single dose treatments. The authors therefore suggested

that an intermediate duration of treatment might be optimal.

We carried out a randomised double blind placebo controlled clinical trial of three days *v* seven days of co-trimoxazole for treating acute uncomplicated urinary tract infection in women.

### Patients and methods

Non-pregnant female patients aged 12-65 presenting to their general practitioner with either dysuria, strangury, or urinary frequency or urgency in the past 24 hours were included in the study. Patients were excluded if they had signs and symptoms of acute pyelonephritis, were known diabetics, had known structural abnormalities of the urinary tract, had indwelling catheters, had recently received immunosuppressive drugs, were allergic to trimethoprim, sulphamethoxazole, or co-trimoxazole, or had received antimicrobial treatment within the previous four weeks. Patients with a known urinary tract infection within the past three months were also excluded. Informed consent was obtained from all participants before enrolment.

Patients were assigned in a random and double blind way to receive either three days of co-trimoxazole 960 mg twice a day followed by four days of placebo twice a day (three day regimen) or seven days of co-trimoxazole 960 mg twice a day (seven day regimen). Blinding was achieved with the double dummy technique by using placebo tablets that looked identical to the active tablets (Bactrimel Forte).

Clean voided urine specimens were obtained from all patients for standard quantitative and dip slide culture tests (Orion Diagnostics, Espoo, Finland) and antimicrobial susceptibility tests. For isolating micro-organisms standard laboratory methods were used. Bacterial counts were performed by the quantitative surface streak technique with a 0.03 ml standard drop on to 7% sheep blood agar and MacConkey agar plates. The isolated micro-organisms were identified by standard bacteriological methods that included the analytic profile index (API Montalieu-Vercieu, France) for Enterobacteriaceae. Coagulase negative staphylococci resistant to novobiocin were identified as *Staphylococcus saprophyticus*. *Escherichia coli* serotyping (for O and K antigens) was carried out with the National Institute for Public Health and Environmental Hygiene (dr Guinée) on the initial and subsequent isolates from most patients whose follow up cultures yielded positive results for *E. coli*. The O and K antigens were identified by bacterial agglutination. Urine samples containing more than two species of bacteria were considered to be contaminated and were not included in the analysis. The presence of growth inhibiting factors was detected by using *Bacillus subtilis* as an indicator strain.

All patients were asked to return to their general

Department of Medical Microbiology, University of Limburg, Box 616, 6200 MD Maastricht, The Netherlands

T A M Trienekens, MD, research fellow  
E E Stobberingh, PHD, associate professor  
R A G Winkens, MD, general practitioner  
A W Houben, BSC, research analyst

Correspondence to:  
Dr Trienekens.

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practitioner one, two, and six weeks after enrolment. On return visits they filled in a questionnaire about relief of symptoms and possible antimicrobial side effects such as headaches, nausea, vomiting, or diarrhoea. In addition, clean voided urine specimens were obtained at each follow up visit and processed in the same way as the initial specimen. Severe side effects were defined as those that needed treatment or that would preclude treatment with co-trimoxazole in the future. From some patients a urine sample was obtained without the questionnaire so the total numbers of patients for whom data on symptoms and bacteriological response were available were different.

Patients were diagnosed as having an urinary tract infection if they presented with acute dysuria, strangury, or urinary frequency or urgency and a bacterial colony count  $\geq 10^5$  colony forming units/ml. The effectiveness of treatment was based on the short and long term effects of cure, persistence, relapse, and reinfection.<sup>11</sup> Persistence was defined as the presence of the causative organism in the urine after treatment had stopped and relapse as the absence of the organism at or after the end of treatment but reappearance of the same organism in the two weeks (early relapse) or six weeks (late relapse) after enrolment. Reinfection was defined as the appearance of another infecting organism in the one or two weeks (early reinfection) or six weeks (late reinfection) after enrolment, whereas cure was defined as absence of the causative organism at and during follow up. Failure of treatment was defined as all cases of persistence, relapse, and reinfection as well as those cases of persistence of symptoms or occurrence of adverse drug reactions for which the doctor had to prescribe another drug. Unassessable cases were those for which evaluating bacteriological response was not possible because no follow up cultures were obtained.<sup>13</sup>

Based on data from our pilot study bacteriuria will be eradicated in 90% of women treated with co-trimoxazole 960 mg twice a day.<sup>14</sup> We took a 10% increase in effectiveness of seven days' treatment over three days' to be the minimum; less would not be clinically meaningful because of the lower costs, greater compliance of patients, and fewer adverse effects associated with shorter treatment. Our null hypothesis was that both treatment with three days' and seven days' co-trimoxazole would be successful in 90% of the patients, and assuming a significance of  $p \leq 0.05$  and a power of 80% we calculated that we required 142 patients for each treatment group.<sup>15 16</sup> The comparisons of treatment regimens and differences in

TABLE III—Cumulative rates of recurrent infections in patients with urinary tract infection treated with co-trimoxazole. Figures are numbers (percentages) of patients

Time after enrolment (weeks)	Length of treatment		p Value
	Three days	Seven days	
1	14/145 (10)	4/152 (3)	0.02
2	19/132 (14)	10/136 (7)	0.10
6	31/139 (22)	23/151 (15)	0.16

TABLE IV—Numbers of patients with recurrent infection in patients with urinary tract infection treated with co-trimoxazole

Type of failure	Length of treatment	
	Three days	Seven days
Persistence	6	4
Early relapse	3	4
Early reinfection	10	2
Late relapse	5	4
Late reinfection	7	9

the prevalence of adverse reactions were tested by  $\chi^2$  analysis.

## Results

Nineteen general practitioners from the south east of The Netherlands participated in the study. From January 1988 to April 1989, 327 women were enrolled in the study: 161 received three days' treatment and 166 seven days' treatment. The mean (SD) ages of both the two groups were 35.0 (4.6) and 38.4 (5.4) years respectively. Follow up cultures at one, two, and six weeks were obtained from 145 (90%), 132 (82%), and 139 (86%) patients receiving the short treatment course and 152 (92%), 136 (82%), and 151 (91%) patients receiving long term treatment respectively.

Table I lists the urinary pathogens isolated. In both treatment groups *E coli* was the most commonly isolated pathogen followed by coagulase negative staphylococci and *Proteus mirabilis*. Other Enterobacteriaceae isolated were klebsiella, citrobacter, and enterobacter. No significant differences were found in the rate of isolation of the uropathogens between the different treatment groups. Table II shows that the proportions of women with acute urinary symptoms whose symptoms were relieved after one, two, and six weeks were similar in both groups. The same applied for the patients with bacteriologically proved urinary tract infection.

The cumulative rates of failure were similar in the two treatment groups, with a slightly higher but non-significant rate in the patients allocated to three days' treatment (table III). Table IV gives the classification of the failure of treatment in both groups. In the group allocated to three days treatment 12 of the 14 *E coli* isolates from follow up cultures in cases of persistence and relapse were similar in serotype or antibiotic susceptibility, or both, to the original infecting micro-organisms; two could not be precisely characterised. The reinfections were caused by *E coli* (six), coagulase negative staphylococci (five), *P mirabilis* (four), and pseudomonas (two). The isolated micro-organisms differed in species, serotype, or antibiogram from the originally infecting strain. *E coli* (10), klebsiella (one), and coagulase negative staphylococci (one) were isolated from samples from cases of treatment failure in patients allocated to (seven) days' treatment. Eight of the 10 *E coli* isolates were similar in serotype or antibiotic susceptibility, or both, to the original infecting strain. The remaining two isolates could not be precisely characterised. The klebsiella and coagulase negative staphylococci were both similar in species and antibiogram. *E coli* and coagulase negative

TABLE I—Numbers (percentages) of patients with urinary pathogens before treatment with co-trimoxazole

Urinary pathogen	Length of treatment	
	Three days (n=161)	Seven days (n=166)
<i>Escherichia coli</i>	90 (56)	83 (50)
Coagulase negative staphylococci	9 (6)	12 (7)
<i>Proteus mirabilis</i>	6 (4)	10 (6)
Other Enterobacteriaceae	6 (4)	6 (4)
<i>Staphylococcus aureus</i>		2 (1)
Negative	48 (30)	53 (32)

TABLE II—Response of symptoms in patients with urinary tract infection treated with co-trimoxazole. Figures are numbers (percentages) of patients

	Symptoms present		Symptoms present and bacteriologically proved	
	Three days' treatment	Seven days' treatment	Three days' treatment	Seven days' treatment
Symptoms absent or improved one week after entry	131/142 (92)	129/145 (89)	88/97 (91)	89/97 (92)
Symptoms absent or improved two weeks after entry	110/121 (91)	108/121 (89)	77/83 (93)	74/81 (91)
Symptoms absent six weeks after entry	97/116 (84)	106/123 (86)	74/85 (87)	72/80 (90)

staphylococci were isolated five times and *Streptococcus faecalis* once; they were different in terms of serotype or antibiogram, or both, from the original isolates. Failure of treatment because of resistance to co-trimoxazole occurred in five patients allocated to three days' treatment and in four allocated to 7 days' treatment.

The compliance of the patients was evaluated by using a questionnaire and by testing the urine specimen for the presence of growth inhibiting factors one week after enrolment. Growth inhibiting factors were found in 10 of the 91 specimens in the group allocated to three days' treatment and in 74 of the 101 specimens in the group allocated to seven days' treatment. Unfortunately, first control specimens taken one week after enrolment were not available from all patients.

Subjective adverse effects occurred in 40 patients (25%) receiving three days' treatment compared with 51 (31%) receiving seven days' treatment ( $p=0.29$ ). These included gastrointestinal upset in 22 (14%) and 34 (20%) patients ( $p=0.137$ ) and allergic reactions in three (2%) and six (4%) patients (table V). Severe side effects occurred in only two patients (one developed rash, one developed gastrointestinal complaints), both of whom had been allocated to seven days' treatment.

TABLE V—Adverse effects of treatment with co-trimoxazole. Figures are numbers (percentages) of patients

Effect	Length of treatment	
	Three days (n=161)	Seven days (n=166)
Nausea	12 (7)	19 (11)
Other gastrointestinal complaints	10 (6)	15 (9)
Vaginal discharge	2 (1)	1 (1)
Rash	3 (2)	6 (4)
Headache	5 (3)	
Others	8 (5)	10 (6)
Totals	40 (25)	51 (31)

## Discussion

Our study protocol fulfilled the 12 methodological criteria mentioned by Philbrick *et al*<sup>6</sup> and the recommendations of Fihn and Stamm<sup>11</sup> to be used in clinical trials of treating uncomplicated urinary tract infections in women. Our results showed no difference in symptomatic response up to six weeks after enrolment between the different treatment regimens either in the group of patients with a bacteriologically proved urinary tract infection or in the group with acute urinary tract symptoms. A similar clinical response was observed in the study of Gossius and Vorland.<sup>18</sup>

The difference in the rate of bacteriological response one week after enrolment might have been due to the presence of growth inhibiting factors in the group allocated to seven days' treatment or to the greater interval after treatment in the group allocated to three days' treatment, enabling early reinfection to occur. Growth inhibiting compounds were found in 74 out of the 101 urine samples from the patients allocated to seven days' treatment. Early reinfection was observed in 10 patients receiving a three days' treatment and in only two patients receiving seven days' treatment. The compliance of the patients allocated to seven days' treatment was 74% as indicated by the presence of growth inhibiting factors in the urine samples. This is similar to the 75% compliance with a treatment regimen of twice a day for about 14 weeks found in the study of Cramer *et al*.<sup>19</sup>

Six weeks after enrolment the cure rates in the groups allocated to three and seven days' treatment were 76% and 83% respectively. These proportions were in general lower than those found in other studies.<sup>6 8 17 18</sup> The difference might have been due to

the fairly short follow up period and the different definitions of cure rate used in other studies. We defined cure rate as relief of initial symptoms plus a sterile urine culture throughout the follow up period. Some investigators used the same definitions but included those patients who were reinfected with a different organism because these patients were cured of the original infection (in our study the so called reinfections).<sup>4-6 8 18</sup> If we used that definition the cure rates were 90% and 92% respectively six weeks after enrolment. These rates are slightly higher than found in the study of Fihn *et al*<sup>12</sup> but lower than those described by Gossius and Vorland.<sup>18</sup>

An important issue for the patient is relief of symptoms. Most patients showed relief after one week. After six weeks most patients were still free of symptoms in both treatment groups. In nine out of 31 bacteriological failures in the group allocated to three days' treatment and five out of 23 bacteriological failures in the group allocated to seven days' treatment, however, the infection was also symptomatic. In the other patients the infection was asymptomatic. In the bacteriologically cured group two patients in the group allocated to three days' treatment and three in the group allocated to seven days' treatment still had complaints of urinary tract infection. The cause of these complaints might have been due to the urethral syndrome caused by organisms such as *Chlamydia trachomatis*.<sup>12</sup> No significant differences in side effects were observed between treatment regimens.

Major adverse effects—that is, enough to stop treatment—occurred only twice in the patients allocated to seven days' treatment. These occurred less often than they did in other studies.<sup>6 12</sup>

Based on our results—that is, the similar symptomatic and bacteriological response six weeks after enrolment and the similar occurrence of adverse effects in the two treatment groups in a study that included an adequate follow up period and a large enough sample to allow statistical analysis—we conclude that three days' treatment with co-trimoxazole is as effective as seven days for the treatment of acute urinary tract infection in non-pregnant women. This study, however, was carried out in patients with more or less similar socioeconomic backgrounds and easy accessibility to well organised medical care. Whether these data could be generalised to other populations from lower socioeconomic backgrounds or with other forms of medical care remains to be elucidated.

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